

What is claimed is:

1. A method for identifying a modulator of PDE10 phosphodiesterase activity, the method comprising:

- (i) obtaining a purified PDE10 having phosphodiesterase activity;
- 5 (ii) incubating the purified PDE10 with a cyclic nucleotide in the presence of a candidate molecule;
- (iii) identifying whether the candidate molecule is a modulator of PDE10 by quantitatively measuring the phosphodiesterase activity of the PDE10 in the presence of the candidate molecule and comparing the activity with PDE10 phosphodiesterase activity in the absence of the candidate molecule.

2. A method for identifying a modulator of PDE10 phosphodiesterase activity, the method comprising:

- (i) obtaining a purified PDE10 and at least one additional phosphodiesterase with phosphodiesterase activity;
- 15 (ii) incubating the purified PDE10 with a cyclic nucleotide in the presence of a candidate molecule and quantitatively measuring the PDE10 phosphodiesterase activity;
- (iii) comparing the PDE10 activity in the presence of the candidate molecule with the activity in the absence of the candidate molecule
- 20 (iv) incubating the at least one additional phosphodiesterase with a cyclic nucleotide in the presence of the candidate molecule and quantitatively measuring the at least one additional phosphodiesterase activity;
- (v) comparing the at least one additional phosphodiesterase activity in the presence of the candidate molecule with the activity in the absence of the candidate molecule;
- 25 (vi) identifying whether the candidate molecule is a modulator with specificity by comparing modulation by the candidate molecule of the of PDE10 activity and of the at least one additional phosphodiesterase activity.

3. A method for identifying a specific modulator of PDE10 according to claim 1, the method further comprising:

- (i) quantitatively measuring at least one additional phosphodiesterase activity in the presence and absence of the candidate molecule; and
- 35 (ii) identifying a specific modulator of PDE10 as one which preferentially modulates the activity of PDE10 compared to the activity of at least one other phosphodiesterase.

4. A method according to claim 1 or 2, wherein the purified PDE10 is purified mammalian PDE10A.

5. A method according to claim 4 wherein the purified PDE10A is purified human PDE10A.

6. A method according to any of claims 1-3, wherein the purified PDE10 is obtained by expression of recombinant DNA.

7. A method according to claim 6, wherein the recombinant DNA is cDNA.
8. A method according to claim 6, wherein the recombinant DNA is genomic DNA.
- 5 9. A method according to claim 6, wherein the recombinant DNA is expressed in cells.
10. A method according to claim 9, wherein the cells are of mammalian, yeast or bacterial origin.
- 10 11. A method according to claim 9 wherein the recombinant DNA is expressed in cells previously subjected to DNA transfection.
12. A method according to claim 10, wherein the cells are lysed before obtaining the purified PDE10.
- 15 13. A method for identifying a modulator of PDE10 according to claim 1 or 2, wherein the cyclic nucleotide is colorimetrically labeled and wherein step (i) further comprises quantitatively measuring a colorimetric change in the presence and absence of a candidate molecule for determining PDE10 activity.
- 20 14. A method for identifying a modulator of PDE10 according to claim 1 or 2, wherein the cyclic nucleotide is fluorescently labeled and wherein step (i) further comprises quantitatively measuring a change in fluorescent signal in the presence and absence of a candidate molecule for determining PDE10 activity.
- 25 15. A method for identifying a modulator of PDE10 according to claim 1 or 2, by use of a marker responsive to changes in PDE10 activity in the presence and absence of a candidate molecule.
- 30 16. A method for identifying a modulator of PDE10 according to claim 1 or 2, wherein the cyclic nucleotide is radiolabeled and wherein step (i) further comprises quantitatively measuring a change in radioactive signal in the presence and absence of a candidate molecule for determining PDE10 activity.
- 35 17. A method for identifying a modulator of PDE10 according to claim 1 or 2, wherein the cyclic nucleotide is radiolabeled cAMP or cGMP and wherein step (i) further comprises quantitatively measuring a change in 8- ^3H -cGMP or 8- ^3H -cAMP hydrolysis in the presence and absence of a candidate molecule for determining PDE10 activity by comparing the radioactive signal of non-hydrolyzed 8- ^3H -cGMP or 8- ^3H -cAMP nucleotides to the
- 40 radioactive signal of the corresponding hydrolyzed nucleosides in the presence and absence of a candidate molecule.
18. A method for identifying a modulator of PDE10 according to claim 1 or 2, wherein the modulator is an inhibitor of PDE10 activity.
- 45 19. A method for identifying a modulator of PDE 10 according to claim 1 or 2, wherein the modulator is an enhancer of PDE10 activity.

20. A method according to claim 1, wherein the modulator acts as a therapeutic agent for a triplet repeat disorder.
- 5 21. A method according to claim 1, wherein the modulator acts as a therapeutic agent suitable for treating at least one of Alzheimer's disease, Parkinson's disease, schizophrenia, depression, anxiety, stress, trauma, and stroke.
- 10 22. A method according to claim 1, wherein the candidate molecule is selected from the group consisting of a small organic molecule, a peptide and an antibody.
23. A method for identifying a modulator of PDE10 using a population of cells, the method comprising:
- 15 (i) providing a population of cells and, optionally, a source of PDE10;
(ii) quantitatively measuring PDE10 activity using the population of cells to establish a first PDE10 activity profile in the absence of a candidate molecule and a second PDE10 activity profile in the presence of a candidate molecule;
(iii) identifying a modulator of PDE10 using the population of cells as one which
20 effects a change in PDE10 activity in the second PDE10 activity profile relative to the first PDE10 activity profile.
24. A method according to claim 23 wherein the PDE10 activity is PDE10A activity.
- 25 25. A method according to claim 23 or 24, wherein the modulator acts as a therapeutic agent for a triplet repeat disorder.
26. A method according to claim 23 or 24, wherein the modulator acts as a therapeutic agent suitable for treating at least one of Alzheimer's disease, Parkinson's disease, schizophrenia, depression, anxiety, stress, trauma, and stroke.
- 30 27. A method according to claim 23 or 24, wherein the candidate molecule is selected from the group consisting of a small organic molecule, a peptide and an antibody.
- 35 28. A method for identifying a modulator of PDE10 according to claim 23 wherein the method further comprises lysing the cells before quantitatively measuring PDE10 activity.
29. A method for identifying a modulator of PDE10 according to claim 23 or 28, wherein the cyclic nucleotide is colorimetrically labeled and wherein step (i) further comprises quantitatively measuring a colorimetric change in the presence and absence of a candidate
40 molecule for determining PDE10 activity.
30. A method for identifying a modulator of PDE10 according to claim 23 or 28, wherein the cyclic nucleotide is fluorescently labeled and wherein step (i) further comprises quantitatively measuring a change in fluorescent signal in the presence and absence of a
45 candidate molecule for determining PDE10 activity.

31. A method for identifying a modulator of PDE10 according to claim 23 or 28, by use of a marker responsive to changes in PDE10 activity in the presence and absence of a candidate molecule.
- 5 32. A method for identifying a modulator of PDE10 according to claim 23 or 28, wherein the cyclic nucleotide is radiolabeled and wherein step (i) further comprises quantitatively measuring a change in radioactive signal in the presence and absence of a candidate molecule for determining PDE10 activity.
- 10 33. A method for identifying a modulator of PDE10 according to claim 23 or 28, wherein the cyclic nucleotide is radiolabeled cAMP or cGMP and wherein step (i) further comprises quantitatively measuring a change in 8-³H]-cGMP or 8-³H]-cAMP hydrolysis in the presence and absence of a candidate molecule for determining PDE10 activity by comparing the radioactive signal of non-hydrolyzed 8-³H]-cGMP or 8-³H]-cAMP nucleotides to the
15 radioactive signal of the corresponding hydrolyzed nucleosides in the presence and absence of a candidate molecule.
- 20 34. A method according to claims 23 or 24, wherein quantitatively measuring PDE10 activity further comprises visualizing the population of cells after incubation with a candidate molecule and measuring changes in the population's physical properties in comparison to a population of cells not treated with a candidate molecule
- 25 35. A method according to claim 23, wherein the population of cells is a population of animal cells.
- 30 36. A method according to claim 35, wherein the animal cells are taken from a transgenic animal.
37. A method according to claim 35, wherein the population of cells is a population of human cells.
- 35 38. A method according to claim 36, wherein the population of cells is a population of human neuronal cells.
39. A method according to claim 35, wherein the population of cells expresses endogenous PDE10.
- 40 40. A method according to claim 36, wherein the population of cells is a population of murine cells.
41. A method according to claim 40, wherein the population of cells is a population of murine neuronal cells.
- 45 42. A method according to claim 41, wherein the population of cells a population of murine striatum cells.

43. A method according to claim 23, wherein the identified PDE10 modulator is an enhancer of PDE10 activity.

5 44. A method according to claim 23, wherein the identified PDE10 modulator is an inhibitor of PDE10 activity.

45. A method for treating an animal subject to a disorder of the basal ganglia with a modulator of a PDE10 the method comprising:

- 10 (i) providing an animal having a disorder of the basal ganglia; and
(ii) treating the animal with an effective amount of a PDE10 modulator in a desired formulation for a prescribed time period such that treatment alleviates symptoms of the disease and/or delays manifestation of the basal ganglia disorder.

15 46. A method for treating an animal according to claim 45 wherein the animal is a human.

47. A method according to claim 45 wherein the disorder of the basal ganglia includes any disorder characterized by a gene defect containing an expanded tract of CAG repeats or expression of gene products containing polyglutamine tracts.

20 48. A method according to claim 47 wherein the disorder of the basal ganglia is Huntington's disease, Alzheimer's disease, Parkinson's disease, schizophrenia, depression, anxiety, stress, trauma, or stroke.

25 49. A pharmaceutical formulation comprising:
an effective amount of a modulator of PDE10 activity in an acceptable carrier.

30 50. A pharmaceutical formulation according to claim 49, further comprising at least one of an emulsifier, a buffer, a glidant, a lubricant, an anti-oxidant, a reducing agent, a colorant, a preservative, a flavoring agent, a filler, or any other appropriate excipient.

35 51. A pharmaceutical formulation according to claim 49 wherein the modulator of PDE10 activity is formulated for delivery including oral, intravenous, subcutaneous, intraperitoneal, intramuscular, brain infusion, brain implantation, transdermal, transmucosal, sustained-release implantation, or any other delivery that is effective for delivery of the modulator of PDE10 activity.

40 52. A pharmaceutical formulation according to claim 49 wherein the acceptable carrier comprises a buffer, a saline solution, dextrose, water, glycerol, ethanol, oil, or combinations thereof.

53. A method for assessing PDE10 activity in an animal model, such animal model being suitable for use in the testing of a disorder of the basal ganglia, the method comprising:
45 (i) providing an animal model of a disorder of the basal ganglia;
(ii) treating the animal model with modulator of PDE10 activity;
(iii) assessing PDE10 activity in the animal model wherein activity is assessed by monitoring at least one of the following relative to a placebo-treated animal and/or a non-treated animal:

(a) a delay in onset of progression of symptoms;

(b) a reversal in manifestation of symptoms;

(c) a lessening of symptoms;

(d) a characteristic change in a disease marker consisting of: a

5 histopathological marker, a biochemical marker including an electrophysiological marker, synaptic remodeling or a change in neuronal function; or a nucleic acid marker including a change in RNA or protein composition, structure, function, and expression;

wherein such change is indicative of disease progression.

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54. A method according to claim 53 wherein the animal model is a model of a disorder of the basal ganglia characterized by a gene defect containing an expanded tract of CAG repeats.

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55. A method according to claim 53 wherein the animal model is a model of Huntington's disease, Alzheimer's disease, Parkinson's disease, schizophrenia, depression, anxiety, stress, trauma, or stroke.

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56. The method of claim 53 or claim 54 wherein the animal is a transgenic animal.

57. The method of claim 53 wherein the modulator of PDE acts by inhibiting PDE10 gene expression.

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58. The method of claim 57 wherein the inhibitor of PDE10 gene expression is antisense RNA or a ribozyme.

59. The method of claim 53 wherein PDE10 consists of PDE10A.

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60. The method of claim 53 wherein the PDE10 modulator is an enhancer or an activator of PDE10 activity.

61. The method of claim 53 wherein the PDE10 modulator is an inhibitor of PDE10 activity.

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